II. REMARKS

A. Status of the Claims

Claims 2, 31-33, 35-51, and 60-61 were pending in the case at the time of the Office Action, with claims 5, 14-17, 23-28, and 34 having been previously withdrawn from consideration as being directed to a non-elected invention. No claims are amended, no new claims are added, and no claims have been canceled. Therefore, claims 2, 31-33, 35-51, and 60-61 are currently under consideration.

B. Declaration Under 37 C.F.R. §1.132

1. The First Declaration of Jerry Bryant Provides Sufficient Actual Proof to Support Applicants' Position that it is Highly Unlikely that 99mTc-EC-Aminopenciclovir Would Be Suitable for Imaging HSV-1 Thymidine Kinase

Applicants' response to the Examiner's position are set forth below in the response to the rejection under 35 U.S.C. §103(a).

2. The Second Declaration of Jerry Bryant Provides Further Actual Proof to Support Applicants' Position that it is Highly Unlikely that 99mTc-EC-Aminopenciclovir Would Be Suitable for Imaging HSV-1 Thymidine Kinase

Applicants' response to the Examiner's position are set forth below in the response to the rejection under 35 U.S.C. §103(a).

C. The Claim Rejections Under 35 U.S.C. §103 Are Overcome

1. The Rejections Based on Iyer in View of Zareneyrizi and Further in View of Yang

Claims 2, 31-33, 35-48, 51, 60, and 61 are rejected under 35 U.S.C. §103(a) as being unpatentable over Iyer *et al.* (J. Nucl. Med., 2001, 42, p. 96-105; hereinafter "Iyer") in view of Zareneyrizi *et al.* (Anti-Cancer Drugs, 1999, 10. p. 685-692; hereinafter "Zareneyrizi") and

further in view of Yang et al. (Ann. Nucl. Med. Sci., 2000, 13, p. 19-36; hereinafter "Yang"). Iyer is said to concern ^{18}F-labeled penciclovir as a probe for imaging HSV1-thymidine kinase reporter gene expression. Zareneyrizi is said to disclose synthesis of ^{99m}Tc-ethylenedicysteine (EC) colchicine to assess tumor microvasculature density. The Examiner argues that one of ordinary skill in the art would be motivated to substitute the ^{18}F label of the penciclovir of Iyer with ^{99m}Tc-EC of Zarencyrizi to lead to ^{99m} Tc-EC-penciclovir. Applicants respectfully traverse.

In rejecting claims under 35 U.S.C. §103(a), the Examiner bears the initial burden of presenting a *prima facie* case of obviousness. See *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). A finding of obviousness requires that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. §103(a). In its recent decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385 (2007), the Supreme Court stated that in setting forth a *prima facie* case of obviousness, it is necessary to show "some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR*, 127 S.Ct. 1727 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

The Examiner has failed to establish a *prima facie* case of obviousness because the Examiner has not set forth sufficient reason with rational underpinning as required by *KSR* to support a *prima facie* case of obviousness. Iyer teaches ^{18}F labeling of penciclovir. There is no rational basis as to why one of ordinary skill in the art would be motivated to replace the ^{18}F of Iyer with ^{99m}Tc-EC of Zareneyrizi. Nothing in Iyer teaches or suggests substituting ^{18}F with a chemical moiety, such as a radiolabeled N_2S_2 chelate, for imaging. Rather, Iyer appears to focus

solely on probes with single atom radiolabels, including ^{18}I, ^{124}I, ^{3}H labeled chemical substrates. In fact, Iyer suggests that substitution with a chemical moiety would not result in an effective reporter, which actually seems to teach away from the claimed invention. For example, on page 97, second full paragraph, Iyer teaches that slight structural variations have a significant effect on biological activity. In particular, Iyer teaches that "the lack of an ether oxygen in the side chain of PCV has a significant effect on its biological properties," even though PCV is "structurally similar to GCV." Page 97, second paragraph. Thus, Iyer actually teaches away from substituting the single atom radiolabel (e.g., 18F) with a substantially larger moiety such as 99mTc-EC.

Furthermore, one of ordinary skill in the art would have understood at the time of the priority date that it would have been highly unlikely for one of ordinary skill in the art to be motivated to substitute the ^{18}F label in the penciclovir of Iyer with ^{99m}Tc-EC of Zareneyrizi because the resulting conjugate (^{99m}Tc-EC-penciclovir) would not be likely to be suitable for imaging HSV1-thymidine kinase reporter gene expression as required by Iyer since it would not be a substrate for HSV1-thymidine kinase.

Applicants have previously submitted the declaration of Mr. Jerry Bryant (Appendix 1; hereinafter "the Declaration"). Mr. Bryant has expertise in the synthesis and use of radionuclide-labeled imaging agents. See Declaration, ¶2-3 and Appendix A of Declaration. Mr. Bryant has declarted that "a person of ordinary skill in the art would not have been motivated to substitute the ^{18}F-labeled penciclovir probe of Iyer *et al.* with 99m-Tc-EC-aminopenciclovir because it is highly unlikely that 99m-Tc-EC-aminopenciclovir would be suitable for imaging HSV1-thymidine kinase reporter gene expression since it would not be a substrate for HSV1-thymidine kinase." Declaration, ¶5.

Mr. Bryant has noted that at the time of the invention, the prior art taught that the acyclic side chain of guanoside analogues such as penciclovir and acyclovir were known to substitute for sugar moieties. Declaration, ¶6. The side chain of Tc-EC-aminopenciclovir does not structurally resemble a sugar moiety or any part of a sugar moiety by virtue of the inclusion of the amino modification of penciclovir and by virtue of binding of EC (a molecule which does not structurally resemble a sugar moiety or part of a sugar moiety) to the amino moiety of aminopenciclovir. *Id.* He cites to information concerning the importance of structural similarity of the side chain to sugar moieties, including Elion *et al.*, Proc. Natl. Acad. Sci. USA, Vol. 74, No. 12, pp. 5716-5720, 1977 (Exhibit 1 of Declaration), Schaeffer *et al.*, J. Med. Chem. 14, 367-369, 1971 (Exhibit 2 of Declaration), and Schaeffer *et al.*, Nature, 1978 Apr 13;272(5654):583-5 (Exhibit 3 of Declaration). Declaration, ¶6.

Furthermore, he notes that a number of acyclic guanosine analogues were known in the field at the time of the filing date of the present patent application. Declaration, ¶7. These structural analogues were known to have acyclic side chains that include at least a portion of a sugar moiety. Cited references providing examples of acyclic guanosine analogues that were known to be substrates for HSV-thymidine kinase that have side chains resembling parts of sugar moieties include De Clercq *et al.*, Nucleosides Nucleotides Nucleic Acids. 2001 Apr-Jul;20(4-7):271-85 (Exhibit 4 of Declaration), Ilsley *et al.*, Biochemistry. 1995 Feb 28;34(8):2504-10 (cited as Exhibit 5 in Declaration, but herein referred to as Exhibit 5a), Golbraikh *et al.*, Nucleic Acids Res. 1989 Oct 11;17(19):7965-77 (cited as Exhibit 5 in Declaration, but herein referred to as Exhibit 5b of Declaration); and Martin *et al.*, J Med Chem. 1986 Aug;29(8):1384-9 (Exhibit 6 of Declaration). Declaration, ¶7.

Thus, Mr. Bryant concludes that "[g]iven this information concerning acyclic guanosine analogues that was known in the field, a person of ordinary skill in the field of the invention would not have been motivated to employ Tc-EC-aminopenciclovir in the method of Iyer et al. to probe for HSV1-thymidine kinase expression." Declaration, ¶8.

The Examiner argues that the previous declaration of Jerry Bryant does not provide sufficient objective evidence to support the argument that a person of ordinary skill in the field of the invention would not have been motivated to employ Tc-EC-aminopenciclovir in the method of Iyer et al. to probe for HSV1-thymidine kinase expression. As set forth above, it is evident that the Declaration provides cited references supporting the declarant's position that Tc-EC-aminopenciclovir would not be a likely substrate for HSV-1 thymidine kinase because the side chain of Tc-EC-aminopenciclovir does not structurally resemble a sugar moiety or any part of a sugar moiety by virtue of the inclusion of the amino modification of penciclovir and by virtue of binding of EC. He cites to information concerning the importance of structural similarity of the side chain to sugar moieties, including Exhibits 1-3. Exhibits 4-6 were cited as teaching a number of structural analogues of TK that include side chains that structurally resemble part of the sugar moiety of thymidine. Clearly, Tc-EC-aminopenciclovir does not structurally resemble any of the substrates of TK set forth in these references. Thus, Mr. Bryant's conclusion that a person of ordinary skill in the field of the invention would not have been motivated to employ Tc-EC-aminopenciclovir in the method of Iyer et al. to probe for HSV1-thymidine kinase expression since it would not be a likely substrate for HSV-1 thymidine kinase is supported by objective factual evidence (i.e., Exhibits 1-6).

Although not required to do so, Applicants, in an effort to advance prosecution of the present matter and to provide further clarification to the Examiner, herein submit the (unsigned)

second declaration (a signed declaration will be forthcoming) of Jerry Bryant providing additional evidence to support patentability of the pending claims (Appendix 2; hereinafter "the Second Declaration"). In the Second Declaration, Mr. Bryant begins by noting, by way of background in paragraph 5, that thymidine kinase catalyzes the transfer of a γ-phosphoryl moiety from ATP to 2'deoxythymidine (dThd) to produce thymidine 5'-monophosphate (dTMP) (reviewed in Tung and Summers, Amtimicrobial Agents and Chemotherapy, Sep. 1994, p. 2175-2179 (Exhibit A) and Omari *et al.*, BMC Structural Biology 2006, 6:22 (Exhibit B)). The reaction scheme is depicted in Exhibit C. As can be seen, thymidine kinase catalyzes the incorporation of a phosphate moiety at the 5-position of the deoxyribose moiety of thymidine.

In paragraph 6, he continues by noting that the available literature at around the time of the filing date of the present patent application teaches that certain molecules that structurally resemble the natural substrate of thymidine kinase can undergo phosphorylation by thymidine kinase. Some of these molecules, such as penciclovir and acyclovir, include an acyclic side chain. The acyclic side chain includes hydroxyl moieties are positioned in a manner that resembles a portion of the deoxyribose moiety of thymidine and in particular that portion that includes the '5 hydroxyl moiety. FPCV is another such example. The hydroxyl moiety of the side chain of FPCV structurally and conformationally resembles that portion of the deoxyribose moiety that includes the 5' hydroxyl moiety (see Exhibit D, which compares the acyclic moiety of FPCV to the deoxyribose moiety of thymidine).

In paragraph 7, Mr. Bryant then observes that 99m-Tc-EC-aminopenciclovir would not be expected by one of ordinary skill in the art to be suitable for imaging HSV1-thymidine kinase reporter gene expression because the available literature suggests that it would not be a good substrate for HSV-1 thymidine kinase. De Winter and Herdewijn (J Med Chem. 1996 Nov

22;39(24):4727-37; Exhibit E) teaches that molecules other than the natural substrate thymidine that are substrates of HSV-1 thymidine kinase are structurally strikingly similar to thymidine. See page 4727 left column and page 4733. 99m-Tc-EC-aminopenciclovir, with its bulky 99mTc-EC moiety and the amino group, is not structurally similar to thymidine. Further, De Winter and Herdewijn teaches that in designing high-affinity nucleoside substrates of HSV-1 thymidine kinase, "care should be taken to maintain the geometry of the base moiety and sugar hydroxyl functionalities." See abstract. A chemical drawing of ^{99m}-Tc-EC-aminopenciclovir is depicted in Exhibit F. As can be seen, in comparison to the chemical diagram of thymidine in Exhibit C, there is loss of a hydroxyl moiety relative to thymidine (and also relative to penciclovir). Thus, Mr. Bryant concludes that in 99m-Tc-EC-aminopenciclovir the geometry of sugar hydroxyl functionalities has clearly not been maintained. He states that these findings are in contrast to FPCV, which does not include a bulky group attached to the acyclic moiety of FPCV and which maintains conformation of the hydroxyl group of the acyclic moiety in the 5' position.

In paragraph 8, Mr. Bryant concludes that, in view of the above, a person of ordinary expertise in the synthesis and use of radionuclidie-labeled imaging agents would not have expected that ^{99m}Tc-EC-aminopenciclovir would be a suitable substrate for HSV1 thymidine kinase or a suitable agent for imaging HSV-1 thymidine kinase reporter gene expression.

Turning back to the rejection, it is further noted that the Examiner has not cited any information to suggest that ^{99m}Tc-EC-penciclovir would be a substrate for HSV-thymidine kinase. The Examiner argues that it was well-known in the diagnostic arts to substitute one reporter probe, or targeting moiety, for another. The Examiner has not cited any evidence to support this assertion. Given that this information appears to be within the knowledge of the

Examiner, Applicants call for a declaration of the Examiner in accordance with 37 C.F.R. §1.104(d)(2).

In contrast to the Examiner's unsupported assertion, Iyer teaches that slight structural variations have a significant effect on biological activity. This teaching in Iyer actually counters the Examiner's assertion. Further, Iyer teaches superiority of penciclovir over ganciclovir in reporting HSV-tk expression in cells, thus clearly teaching that moieties, whether for reporting or targeting, are indeed not so interchangeable. Thus, the Examiner's position is not supported by the evidence of record.

In view of the foregoing, it is respectfully submitted that the Examiner has failed to establish a *prima facie* case of obviousness. No reasonable basis with rational underpinnings has been set forth for why one of ordinary skill in the art, in view of the teachings of these references, would combine the reference teachings to lead to the claimed invention because these references actually teach away from the claimed invention. Applicants therefore respectfully request withdrawal of the rejection under 35 U.S.C. §103(a) based on Iyer in view of Zareneyrizi and further in view of Yang.

2. The Rejections Based on Iyer in View of Zareneyrizi and Yang, and Further in View of Belinka

Claims 2, 31-33, 35-51, 60, and 61 are rejected under 35 U.S.C. §103(a) as being unpatentable over Iyer (as above) in view of Zareneyrizi (as above) and Yang (as above), and further in view of Belinka (U.S. Patent 5,609,847; hereinafter "Belinka"). The teachings of Iyer, Zareneyrizi, an Yang are as discussed above. The Examiner adds in Belinka to provide a teaching concerning kits and inclusion of gluconate or glucarate as transition chelators. Applicants respectfully traverse.

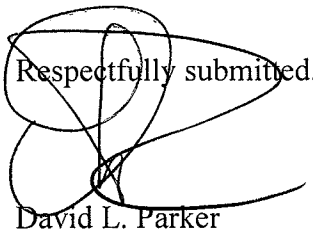
For the reasons set forth in the foregoing section, herein incorporated by reference, Iyer in view of Zareneyrizi and Yang fails to disclose the N_2S_2 chelate-targeting ligand conjugates as set forth in claim 2. Belinka fails to remedy the deficiencies of these references because it is only cited as teaching kits that include glucarate and gluconate, two transition chelators, and interchangeability of certain chelators. Without concurring with the Examiner regarding the teachings of Belinka, Applicants note that Belinka fails to provide the missing motivation to provide for the chelator-targeting ligand conjugates as set forth in claim 2. Thus, Belinka fails to remedy the deficiencies of Iyer, Zareneyrizi, and Yang.

In view of the foregoing, it is respectfully submitted that the Examiner has failed to establish a *prima facie* case of obviousness. No reasonable basis with rational underpinnings has been set forth for why one of ordinary skill in the art, in view of the teachings of these references, would combine the reference teachings to lead to the claimed invention. Applicants therefore respectfully request withdrawal of the rejection under 35 U.S.C. §103(a) based on Iyer in view of Zareneyrizi and Yang, and further in view of Belinka.

D. Conclusion

In view of the foregoing, it is respectfully submitted that each of the pending claims is in condition for allowance, and a Notice of Allowance is earnestly solicited. The Examiner is invited to contact the undersigned attorney at (512) 536-3055 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



David L. Parker
Reg. No. 32,165
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
512.474.5201 (telephone)
512.536.4598 (fax)

Date: May 4, 2010